PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* 23 August 2005 (23-08-2005)

Applicant's or agent's file reference
793-104PCT2

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2005/000491	01 April 2005 (01-04-2005)	01 April 2004 (01-04-2004)

International Patent Classification (IPC) or both national classification and IPC
IPC(7): C12N 15/63, C12Q 1/68

Applicant
NOVATION PHARMACEUTICALS INC. ET AL

1. This opinion contains indications relating to the following items :

- [X] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [X] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [X] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**
If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA	Date of completion of this opinion	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	23 August 2005 (23-08-2005)	Kristoffer Wilde (819) 953-0551

Box No. I **Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

   [X] the international application in the language in which it was filed

   [ ] a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      [X] a sequence listing

      [ ] table(s) related to the sequence listing

   b. format of material

      [X] on paper

      [X] in electronic form

   c. time of filing/furnishing

      [X] contained in the international application as filed.

      [X] filed together with the international application in electronic form

      [ ] furnished subsequently to this Authority for the purposes of search.

3 [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statement that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments :

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	none	YES
	Claims	1-22	NO
Inventive step (IS)	Claims	none	YES
	Claims	1-22	NO
Industrial applicability (IA)	Claims	1-22	YES
	Claims	none	NO

2. Citations and explanations :

Reference is made to the following documents:

D1: WO 00 39314 A1 (NOVATION PHARMACEUTICALS INC.)
6 July 2000 (06-07-2000)

D2: WO 00 38674 A1 (NOVATION PHARMACEUTICALS INC.)
6 July 2000 (06-07-2000)

D3: KASTELIC T ET AL: "Induction of rapid IL-1β mRNA degradation in THP-1 cells mediated through the AU-rich region in the 3'UTR by a radicicol analogue", CYTOKINE. October 1996, Vol. 8, No. 10, pages 751-761

D4: YEILDING N ET AL: "Coding elements in exons 2 and 3 target c-myc mRNA downregulation during myogenic differentiation", MOLECULAR AND CELLULAR BIOLOGY. May 1997, Vol 17, No. 5, pages 2698-2707

D5: ROSS J ET AL: "mRNA stability in mammalian cells", MICROBIOLOGICAL REVIEWS. September 1995, Vol. 59, No. 3, pages 423-450

Novelty - Article 33(2) PCT

The problem to be solved by the instant application is the provision of an assay for identifying compounds which affect the stability of mRNA. In accordance with the assay, DNA expression vectors, host cells, cell lines, methods of screening, assay systems and kits are claimed.

Document D1 discloses a method for the identification of compounds which affect mRNA stability. Document D1 discloses a DNA expression vector comprising a coding sequence for a detectable signal (e.g. luciferase) under operative control of a promoter and a 3' UTR, wherein an mRNA instability sequence (e.g. the AU-rich element from the 3'UTR of IL-1β) is inserted (see pages 3-7 and figure 3). Further, they disclose host cells and cell lines comprising said vector (see page 6, lines 3-15) and assays for identifying compounds which affect the stability of mRNA. They also disclose the use of a control in the assay, wherein the control is the expression vector without the mRNA instability sequence or the expression vector in the absence of the test compound (see page 7, line 20- page 8, line 20). The control vector can alternatively be present in the same cell as the DNA expression vector, wherein a different detectable protein is used in the control as opposed to the expression vector (see page 8, lines 14-20). Finally, the assay was adapted to 96 well plates for high throughput (see page 11, lines 18-29). Accordingly, claims 1-4 and 6-22 do not meet the criteria for patentability under Article 33(2) PCT.

Continued in Supplemental Box.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

Claim defects:

Claims 1, 9, 10, 14, 15, 18 and 19 are not compliant with Article 6 PCT. Said claims are objectionable in that the "mRNA instability sequence" is merely defined in terms of a desired result rather than by the technical features of the sequence necessary to achieve that result.

Claim 9 is not compliant with Article 6 PCT. As worded, it is not clear if the detectable signal of the second protein is different from, or the same as, that of the first protein.

Claim 10 is not compliant with Article 6 PCT. In step (iv), the "control" must be clearly defined before measured detectable signals can be compared.

Claim 18 is not compliant with Article 6 PCT. "High throughput" is a relative term without a frame of reference.

Description defects:

In the brief description of the drawings on page 7 of the instant application, there is a reference to a 30 bp fragment in figure 2; however, the fragment in figure 2 appears to be 40 bp, not 30 bp. Accordingly, the description is no compliant with Article 5 PCT.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of : Box No. V

Novelty - Article 33(2) PCT (continued)

Document D2 discloses a method for the identification of compounds which affect mRNA stability. Document D2 discloses a DNA expression vector comprising a coding sequence for a detectable signal (e.g. luciferase) under operative control of a promoter and a 3' UTR, wherein an mRNA instability sequence (e.g. the AU-rich element from the 3'UTR of IL-1β) is inserted (see page 22, lines 5-14 and figure 2). Further, they disclose host cells and cell lines comprising said vector (see page 22, lines 16-26) and assays adapted to 96 well plates for identifying compounds which affect the stability of mRNA (see page 23-page 27). Accordingly, claims 1-4, 6-8, 10-16 and 18-21 do not meet the criteria for patentability under Article 33(2) PCT.

Document D3 discloses an expression system comprising a luciferase gene containing the AU-rich elements of the IL-1β 3'UTR and cells transformed with said expression system (see page 758, second paragraph). Accordingly, claims 1-4 and 6-8 do not meet the criteria of patentability under Article 33(2) PCT.

Document D4 discloses an expression vector for transfecting cells comprising a gene encoding a detectable protein (e.g. CAT) under the operative control of a MLV-LTR promoter and a *c-myc* coding region instability determinant (CRD) introduced 3' to the gene encoding the detectable protein (see figure 1). Accordingly, claims 1-8 do not meet the criteria of patentability under Article 33(2) PCT.

Inventive Step - 33(3) PCT

Given the lack of novelty in claims 1-22 according to Article 33(2) PCT, said claims also lack an inventive step under Article 33(3) PCT.

It should be noted that amending the claims so that the "mRNA instability sequence" was limited to CRDs would still not result in claims compliant with Article 33(3) PCT. Document D5 is a review article summarizing the known aspects of mRNA stability in mammalian cells. Document D5 reviews what is know about *cis*-acting sequence determinants of mRNA stability from both the 3'UTR (e.g., AU-rich elements) and the mRNA coding region (e.g., CRDs) (see pages 428-432). Given what was known of *cis*-acting sequence determinants, it would be trivial for one skilled in the art to apply any known *cis*-acting sequence determinants of mRNA stability to the methods and assays of D1. Therefore, the subject matter of claims 1-22, as it pertains to CRDs, is not compliant with Article 33(3) PCT in view of documents D1 and D5.

Industrial Applicability - Article 33(4) PCT

Claims 1-22 appear to define subject matter that has industrial applicability under Article 33(4) PCT, based on the use of a DNA expression vector comprising a coding sequence for a detectable signal under operative control of a promoter and a 3' UTR, wherein an mRNA instability sequence is inserted for use in an assay for identifying compounds which have an effect on mRNA stability.